FORM PTO-1390 (REV 11-98) U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: 113737.5

US APPLICATION NO (If known see 37 CFR 1 5): 09/647910

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/02059	26 March 1999 (26.03.99)	06 April 1998 (6.04.98)

TITLE OF INVENTION
APPARATUS AND METHOD FOR TAKING SAMPLES FROM POLYMER SUPPORT MATERIALS

APPLICANT(S) FOR DO/EO/US
Gauss, Christine; Horn, Martin; Kalkum, Markus; and Eickhoff, Holger

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND or SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Postcard
    Certificate of Express Mailing

U.S. APPLICATION NO. (if known see 31 CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUUMBER
09/647910	PCT/EP99/02059	113737.5

17. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5))		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00		
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $760.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 1,000.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(c)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	15 -20 =	0	X $18.00	$ 0.00	
Independent claims	2 -3 =	0	X $78.00	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+$260.00	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$	
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 0.00	
SUBTOTAL =				$ 1,130.00	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 1,130.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00	
TOTAL FEES ENCLOSED =				$	
				Amount to be: refunded	$
				charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [X] Please charge my Deposit Account No. 500436 m the amount of $ 1,130.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 500436 A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Robert A. Koons, Jr.
Pepper Hamilton LLP
18th and Arch Streets
3000 Two Logan Square

Philadelphia, PA 19103-2799

SIGNATURE

Robert A. Koons, Jr.
NAME

32,474
REGISTRATION NUMBER

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re: Attorney Docket No. 113737.5

In re application of: Gauss, Christine; Horn, Martin; Kalkum, Markus; and Eickhoff, Holger
Serial No.: Not Yet Assigned **Group Art Unit: Not Yet Assigned**
Filed: Herewith **Examiner: Not Yet Assigned**
For: APPARATUS AND METHOD FOR TAKING SAMPLES FROM POLYMER SUPPORT MATERIALS

Box PCT
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

Prior to an examination on the merits, kindly amend the application as follows:

IN THE ABSTRACT

Please delete "(Fig. 1)" on line 11.

IN THE CLAIMS

Please enter the following amendments:

1. (Amended) A sample taking apparatus, arranged for receiving a plurality of samples from a support material (40), [characterized in that] comprising a plurality of separation tools (10) for taking the samples from the support material (40) [are provided], wherein the separation tools (10) are arranged on a holding device (20) and are provided with respective actuating means (30), by which the separation tools (10) can be separately controlled and actuated.

4. (Amended) The sample taking apparatus according to [one of the preceding claims] claim 1, wherein the actuating means (30) are [pneumatic or hydraulic

cylinders (31 to 38) or piezoelectric or electromagnetic actuating devices] selected from the group consisting of pneumatic cylinders, hydraulic cylinders (31-38), piezoelectric actuating devices, and electromagnetic actuating devices.

5. (Amended) The sample taking apparatus according to [one of the preceding claims] claim 1, wherein the separation tools (10) are arranged on the holding device (20) [in rows or] in a matrix having at least one row.

7. (Amended) The sample taking apparatus according to [one of the preceding claims] claim 1, wherein each separation tool (10) is connected by a guide means (21) to the respective actuating means (30), wherein each guide means (21) has a connecting opening (21a) [via which] whereby the separation tool is connected to a pressure system.

8. (Amended) The sample taking apparatus according to [one of the preceding claims] claim 1, wherein the holding device (20) is connected to an adjusting device (200) for positioning the holding device (20) with the separation tools (10) in a horizontal or x-y reference plane.

9. (Amended) The sample taking device according to claim 8, [including] further comprising an imager (300) and a control device (400), wherein the imager (300) supplies image data of a support material[, from which the samples are to be taken,] to the control device, which is arranged to generate target coordinates for controlling the adjusting device (200).

10. (Amended) [A method for taking samples, wherein samples are cut from a support material (40) and transferred onto a target substrate (50), characterized in that cutting of the samples is carried out successively in time while using a sample taking apparatus (100) having a plurality of separation tools (10) being separately controlled and

actuated and in that that the transfer of the removed samples onto the target substrate (50) is carried out parallel in time.] A method for cutting samples from a support material (40) and transferring said samples onto a target substrate (50), said method comprising:

cutting said samples successively in time using a sample taking apparatus (100) having a plurality of separation tools (10) that are separately controlled and actuated; and

transferring said samples onto said target substrate (50) simultaneously in parallel.

13. (Amended) The method according to [one of the claims 10 through 12] claim 10, wherein the separation tools (30) are actuated by compressed air or a hydraulic liquid.

14. (Amended) The method according to [one of the claims 10 through 13] claim 10, wherein the support material is a separation gel and the samples are substance bands (41, 42, 43) distributed in the separation gel, and [being transferred onto a microtiter plate (50) provided as the target substrate.] the target substrate is a microtiter plate (50).

15. (Amended) The method according to [one of the claims 10 to 14, wherein the separation tools (30) with the removed samples are subject to underpressure and, for the transfer onto the target substrate, with overpressure.] claim 10, further comprising the steps of:

applying an underpressure to the separation tools containing removed samples prior to the transfer; and

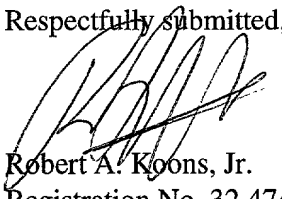
applying an overpressure to the separation tools containing removed samples to effect the transfer to the target substrate.

REMARKS

Claims 1-15 amended to eliminate multiple dependency included in the claims, and to conform with U.S. Practice.

We look forward to a favorable action on the merits at an early date.

Respectfully submitted,



Robert A. Koons, Jr.
Registration No. 32,474
Attorney for Applicant

Dated: October 6, 2000

PEPPER HAMILTON LLP
3000 Two Logan Square
Eighteenth and Arch Streets
Philadelphia, PA 19103-2799
Telephone (215) 981-4406

Practitioner's Docket No. 113737.5 *PATENT*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Gauss, Christine; Horn, Martin; Kalkum, Markus; and Eickhoff, Holger

Application No.: Not Yet Assigned
Filed on: Herewith
Title: APPARATUS AND METHOD FOR TAKING SAMPLES FROM POLYMER SUPPORT MATERIALS

STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) and 1.27(b)--NONPROFIT ORGANIZATION

I hereby state that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of Nonprofit: Max-Planck-Gesellschaft zur Foerderung der Wissenschaften e.V.
Address of Nonprofit: Hofgartenstrasse 8
D-80539 Munich
Germany

TYPE OF NONPROFIT ORGANIZATION

Would Qualify as Nonprofit Scientific or Educational Under Statute of State of the United States of America if Located in the United States of America.

I hereby state that the nonprofit organization identified above qualifies as a nonprofit organization, as defined in 37 CFR 1.9(e), for purposes of paying reduced fees to the United States Patent and Trademark Office under Sections 41(a) and (b) of Title 35, United States Code, with regard to the invention described in the specification filed herewith, with title as listed above.

I hereby state that rights under contract or law have been conveyed to, and remain with, the nonprofit organization, with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed below and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 C.F.R. 1.9(c), if that person made the invention, or by any concern that would not qualify as a small business concern under 37 CFR 1.9(d), or a nonprofit organization under 37 CFR 1.9(e)

Each such person, concern, or organization having any rights in the invention is listed below.

No such person, concern, or organization exists.

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

SIGNATURE Christa Herzog Date 14.11.2000

By: Christa Herzog
(Type or Print Name)

Title: Head of Patent Department

Address: Hofgartenstr. 8, 80539 München

14611/US Hz/hr

Apparatus And Method For Taking Samples From Polymer Support Materials

The invention relates to a sample taking apparatus which is configured to receive or transfer a plurality of samples from polymer support materials, and a method for use of such a sample taking apparatus. The invention relates, in particular, to taking samples by separating partial areas with certain substances from the support materials, such as, for example, punching of substance bands from separation gels.

From chemistry, biology, medicine, and molecular biotechnology numerous separation methods are known in general in which substance mixtures in a support medium are substance-specifically spatially separated and, subsequently, are subjected to further processing steps. In the field of genome research, for the separation of, for example, protein mixtures, genome sequences or DNS mixtures, electrophoretic separation methods with one or more dimensional separation gels are used.

In the two-dimensional gel electrophoresis, for example, proteins are separated according to their acid or base characteristic in a first dimension by means of a first separation step and in a second dimension as a function of size by means of a second separation step. As a result, the separated fragments are located in a so-called two-dimensional gel which has the form of a gel layer of a surface area of approximately 8 cm x 12 cm to 20 cm x 30 cm and a thickness of approximately 0.5 mm to 1 mm. After separation, the fragments are dyed for the purpose of visualization with organic (conventional dyes such as, for example, Coomassie blue, fluorescent dyes) or inorganic (for example, silver staining) substances so that bands, blots, or irregularly shaped spots are formed. In the following, the separated fragments in a support medium are

generally referred to as bands. The bands are irregularly distributed in the two-dimensional gel depending on the substance properties. For further processing or analysis of the separated fragments, the bands in the past have been cut out manually or semi-automatically by means of a scalpel from the gel in order to then perform specific further examinations, for example, by mass spectrometry.

In the aforementioned applications in genome research but also, for example, in the modern combinatorial chemistry, there is an interest to separate in time periods as short as possible a number of substances as large as possible and to further process the separated fragments or samples. The separation technique as well as the further analytical examination of the samples nowadays provide for a high sample throughput. The transfer of separated fragments onto substrates, which represent the starting point for further processing, however, represents a bottleneck to this day.

It is an object of the invention to provide an apparatus and a method for taking samples, which are improved so as to allow a greater number of samples being simultaneously processed. The invention is particularly directed to applications in the gel electrophoretic separation methods.

This object is solved by an apparatus and a method including the features according to claims 1 and 10, respectively. Preferred embodiments of the invention are apparent from the dependent claims.

The basic idea of the invention resides in the provision of a sample taking device with a plurality of individually actuatable separation tools which are commonly movable in a reference plane at a spacing from the material from which samples are to be taken, and are selectively movable or actuatable toward the material. The sample separation from the material is carried out preferably serially. This means

that the sample taking device is moved always alternating to a certain position in the reference plane, and then one of the separation tools for sample loading is actuated. For movement in the reference plane the sample taking device is provided with an adjusting device. The sample transfer onto a target substrate can then be carried out simultaneously and parallel from all separation tools.

The control of the sample taking device is carried out preferably in combination with an image taking system. The image taking system comprises a camera device with which the sample positions (for example, band positions) are detected. Based on the sample positions, the target coordinates for each movement of the adjusting device are derived. The combination of a sample taking device (with a plurality of separation tools) with an image taking device is an important feature of the invention because this makes possible an automated operation and acceleration of the entire sample taking process.

The invention is generally usable in all processes in which samples are to be taken from a support or sample material and transferred onto a target substrate. The term sample taking therefore in general refers to the separation (for example, cutting, punching, stamping or the like) of the sample from the material and the placement of the separated sample in a predetermined way on a target substrate. The invention can be carried out especially beneficially with polymer support materials (layer-shaped or volume-shaped) or with other materials (for example, membranes or biological materials such as cell clusters arranged on substrates). The target substrate is preferably a microtiter plate. A preferred application of the invention resides in the controlled removal of samples from separation gels, wherein the removal positions are determined by image processing in a predetermined way and wherein the advancing to the removal positions and the

sample removal by means of the separation tools (punching capillaries) are carried out sequentially, and in the transfer of the taken samples into the depressions of a microtiter plate, wherein a temporally parallel sample deposition in the depressions is provided for the transfer.

Further details and advantages of the invention are described in the following with reference to the Figures, showing:

Fig. 1 a perspective view of a sample taking device according to the invention; and

Fig. 2 a schematic overview representation for illustrating the method according to the invention.

The invention will be described in the following with reference to a sample taking apparatus with a row of separation tools which comprise eight capillary-shaped punching tools. The invention, however, is not limited to this embodiment but can be implemented with separation tools shaped differently, with separation tools arranged like a matrix with rows and columns, or with separation tools whose number changes depending on the application.

The sample taking apparatus 100 according to the invention comprises according to Fig. 1 a plurality of separation tools 10, a holding device 20, and a plurality of actuating means 30.

The separation tools 10 comprise tubular punching or stamping tools, for example, in the form of punching capillaries 11 through 18. As an alternative, other cutting tools can be provided also. Each punching tool is connected at one end with a guide portion 21 of the holding device 20 so as to be moveable in the axial direction. At the other end of each punching tool a cutting edge is provided. The

cross-sectional shape, the geometric dimensions, and the relative arrangement of the punching tools are determined based on the application. For sample taking on separation gels, each punching tool is preferably formed by a capillary at whose end the cutting edge is provided by the end of the capillary wall. The inner diameter of the capillary is selected based on the application and is preferably less than the thickness of the material (separation gel, membranes or the like) from which the sample is to be taken. For conventional two-dimensional separation gels, the inner diameter is preferably approximately 0.5 to 2 mm, for example, approximately 1 mm. The thickness and the material of the capillary wall are selected in order to provide a sufficient resistance for the separation step. The capillaries can be comprised of an inert material such as, for example, metal, glass, ceramic or plastic material. Steel capillaries are preferred because of their high resistance. The relative spacing between the capillaries is adjusted depending on the application based on the conditions of the target substrates. When the target substrates is, for example, a microtiter plate (see Fig. 2), the capillary spacing corresponds to the reservoir spacing of the microtiter plate (for example. 9 mm).

The holding device 20 is comprised of guide parts 21, a connecting plate 22 and a holding plate 23. The connecting plate 22 is provided with an adjusting device (not shown) for connecting the holding device 20. The adjusting device is configured for movement of the sample taking device into a reference plane to certain target coordinates, as will be explained infra. The holding plate 23 serves as a common holder for the guide parts 21 and the actuating means 30 and for the connecting plate 22.

For each separation tool (for example, for each capillary) a guide part 21 is provided which has a double function.

Firstly, by means of the guide part 21 an axial movability of the separation tools from a basic position into a punching position is determined. Moreover, each guide part 21 contains a connecting opening 21a via which the respective separation tool can be loaded by pressure, or alternatively vacuum, by means of a pressure system (not represented). The vacuum serves to secure the punched-out sample in the separation tool. When it is desired to place the samples onto the target substrate, the vacuum is replaced with a slight overpressure (in any case, for example, approximately 1/2 technical atmosphere). The connecting opening 21a can moreover be used for supplying a rinsing liquid.

For preventing sample migration in the capillary, a retaining device can be provided inside thereof which separates a sample volume at the end of the capillary from the remainder of the capillary and which can be formed, for example, by a pin in the capillary.

The actuating means 30 comprise a group of pneumatic cylinders 31, 32, ..., 38 each associated to a respective separation tool. The pneumatic cylinders are operated by compressed air and include electrical switching valves, respectively. When a certain pneumatic cylinder is activated by actuation of the electrical switching valve, the corresponding separation tool is moved in the axial direction by an advancing stroke. After completion of the punching process, the separation tool is returned due to the action of an internal spring element or an external restoring spring or equally by pressure application. An important advantage of the invention is that the separation tools or punching tools can be individually controlled so that the sample taking can be adjusted to any type of sample format.

Instead of the pneumatic cylinders, the actuating means 30 can comprise other drive elements, for example, hydraulic (with hydraulic cylinder), piezoelectric or electromagnetic drives.

The holding device 20 is connected to the adjusting device such that the direction of axial movement of the cutting tools is substantially perpendicularly to the (movement) reference plane of the adjusting device.

A sample taking method is explained in the following with reference to Fig. 2. Fig. 2 shows schematically the sample taking device 100 in different method phases as well as the adjusting device 200, an imager 300, and a control device 400 in an example of taking a sample from a separation gel 40. Essentially known arrangements based on so-called „spotting and picking" robots can be used as the adjusting and control devices. The control device 400 sends to the adjusting device 200 respective target coordinates to which the sample taking device 100 is to be moved. The target coordinates are obtained as follows by means of the imager 300. As a separation gel 40 a two-dimensional gel on a planar substrate is illustrated as an example. As an alternative, the invention can also be implemented correspondingly with a one-dimensional gel, for example, in a layer or band shape.

The image taking device 300 comprises a camera (not shown) for obtaining a digital image of the two-dimensional gel 40 with the regularly or irregularly arranged dyed bands 41. The camera is preferably connected, like the sample taking device, with the adjusting device and is movable above the two- dimensional gel in the reference plane (x-y plane) parallel to the plane of the gel 40. The digital image is processed in the control device 400. The image evaluation advantageously is not necessarily referring to defined markings on the separation gel substrate but to the

separate bands or spots in the separation gel. With the invention it was possible to demonstrate for the first time that these bands or spots, which have a variable contrast relative to the surroundings, are also suitable for image taking and evaluation. For larger size bands or spots it is even possible to provide several punching steps (for example, spot diameter 2 mm, punching capillary diameter approximately 1 mm: 2 to 3 punching steps per spot). In the control device a program sequence is provided which, as a function of the size of the band, determines the target coordinates and determines how often adjacent gel pieces are to be taken from a band. The target coordinates refer to the position of the sample taking device 100 relative to a band in the two-dimensional gel while considering the relative coordinates of the punching capillary respectively to be selected. An important aspect of the invention is that, after image taking and processing or evaluation, a desired one of the samples is automatically taken in a time sequence with the punching capillaries from the separation gel. Advantageously, the entire image recognition can be carried out automatically. An operator-controlled camera control is not a compulsory requirement. According to the separation result, the punching positions are irregular based on the application and are not distributed according to a predetermined pattern. By using the imager 300, which serves as an optical positioning device, a target-oriented punching is possible even for irregular band or spot distribution.

By means of the adjusting device 200, the sample taking apparatus is arranged such that the spacing of the punching capillaries, in its basic position, from the substrate on which the gel is located corresponds substantially to the advancing distance of the actuating means (see supra).

After taking the digital image and determining the target coordinates, the sample taking device 100 is first moved

into the first position P1 in which one of the punching capillaries (for example, 11) is aligned relative to a certain band 42 in the separation gel. As soon as the position P1 has been reached, the pneumatic cylinder 31 is actuated so that the punching capillary 11 is shot into the gel and the sample is received at the capillary end. Subsequently, the adjusting device 200 moves the sample taking device 100 to the next position P2 where the same process is repeated with the next punching capillary (for example, 12). The position P2 can relate to a different sample in the same band 42 or in another band 43. In this way, the positions P1 to P8 are approached according to the number of punching capillaries (P3 to P8 are not shown). The punching capillaries are therefore sequentially loaded at the positions P1 to P8. The sequentially loaded punching capillaries must not necessarily be loaded in the sequence of their arrangement.

Subsequently, when all or some punching capillaries, depending on the application, are loaded, the sample taking device is moved to the target substrate, for example, in the form of a microtiter plate 50. The sample taking device 100 is positioned such that the ends of the punching capillaries are positioned opposite the respective reservoirs of the microtiter plate 50. The individual samples are deposited in the reservoirs by application of pressure to the punching capillaries. The deposition of the samples on the microtiter plate 50 is carried out across all punching capillaries simultaneously, i.e. parallel. The deposition of the samples is advantageously sample-specific. This means that each individual sample or group of samples corresponding to a common band is deposited separately in individual reservoirs. The samples are transferred into an ordered grid for further assay or analysis. Subsequently, optionally with interposition of a cleaning step in a cleaning bath 60, the next sequence of sample taking on the sample substrate 40 is carried out.

The sequential sample taking with the punching capillaries and the parallel sample deposition are repeated as many times as it takes to punch out all bands on the separation gel.

The system illustrated in Figs. 1 and 2 can be modified in that not a straight row of separation tools but a curved row or a matrix arrangement of separation tools is provided. Moreover, it can be arranged such that during the sample taking sequence several sample pieces are taken up in sequence by a punching capillary. It is even possible with a correspondingly matched sample deposition that in one punching capillary several samples of different bands are received. In the case of multi-loading of the punching capillaries, it can be provided that between the samples separation pieces, for example, from a gel area without sample, are taken. Finally, it is possible that at one position (P1, P2, ...) optionally several punching capillaries can be actuated simultaneously.

The sample taking system according to the invention has the advantage that punching speeds on the separation gels of approximately 1000 samples per hour can be reached. This greatly surpasses conventional punching speeds with manual or semi-automatic punching devices of approximately 200 samples per hour. The sample taking can be automated. The high punching speed has the additional advantage that the punching of, for example, a two-dimensional separation gel with more than 1000 proteins can be finished before the separation gel possibly has changed geometrically as a function of time and thus would exclude a further reproducible processing.

CLAIMS

1. A sample taking apparatus, comprising a plurality of separation tools (10) on a holding device (20), wherein the separation tools (10) are provided with respective actuating means (30), by which the separation tools (10) can be controlled separately.

2. The sample taking apparatus according to claim 1, wherein the separation tools are tubular punching tools (11 to 18) which at one end thereof are axially movably arranged on the respective actuating means (31 to 38) and have, at the other end thereof, a punching edge.

3. The sample taking apparatus according to claim 2, wherein the punching tools (11 to 18) are formed as capillaries.

4. The sample taking apparatus according to one of the preceding claims, wherein the actuating means (30) are pneumatic or hydraulic cylinders (31 to 38) or piezoelectric or electromagnetic actuating devices.

5. The sample taking apparatus according to one of the preceding claims, wherein the separation tools (10) are arranged on the holding device (20) in rows or in a matrix.

6. The sample taking apparatus according to claim 5, wherein the separation tools (10) are arranged such that their ends form an array which corresponds to the array of sample reservoirs in a predetermined microtiter plate format.

7. The sample taking apparatus according to one of the preceding claims, wherein each separation tool (10) is

connected by a guide means (21) to the respective actuating means (30), wherein each guide means (21) has a connecting opening (21a) via which the separation tool is connected to a pressure system.

8. The sample taking apparatus according to one of the preceding claims, wherein the holding device (20) is connected to an adjusting device (200) for positioning the holding device (20) with the separation tools (10) in a x-y reference plane.

9. The sample taking device according to claim 8, including an imager (300) and a control device (400), wherein the imager (300) supplies image data of a support material, from which the samples are to be taken, to the control device arranged to generate target coordinates for controlling the adjusting device (200).

10. A method for taking samples, wherein from a support material (40) samples are cut out and transferred to a target substrate (50), wherein cutting of the samples is carried out successively in time while using a sample taking device (100) having a plurality of separation tools (10), and wherein the transfer of the taken samples onto the target substrate (50) is carried out parallel in time.

11. The method according to claim 10, wherein alternatingly first the sample taking apparatus (100) is moved by an adjusting device (200) into a position (P1, P2, ...) corresponding to predetermined target coordinates and then one or more separation tools (31 to 38) are actuated until all or some separation tools (31 to 38) are loaded with removed samples, whereupon the sample taking device (100) is moved to the target

substrate (50) and the samples are transferred from the separation tools onto the target substrate (50).

12. The method according to claim 11, wherein the target coordinates of the positions (P1, P2, ..) are obtained from image data of the support material (40).

13. The method according to one of the claims 10 through 12, wherein the separation tools (30) are actuated by compressed air or a hydraulic liquid.

14. The method according to one of the claims 10 through 13, wherein the support material is a separation gel and the samples are substance bands (41, 42, 43) distributed in the separation gel, and being transferred onto a microtiter plate (50) provided as the target substrate.

15. The method according to one of the claims 10 to 14, wherein the separation tools (30) with the removed samples are subject to underpressure and, for the transfer onto the target substrate, with overpressure.

ABSTRACT

A sample taking apparatus comprises a plurality of separation tools (10) (for example, punching capillaries) on a holding device (20), wherein the separation tools (10) are each provided with actuating means (30) for separate control thereof. In a sample taking method (for example, for punching samples from separation gels), successively removed samples are deposited in parallel onto a target substrate.
(Fig. 1).

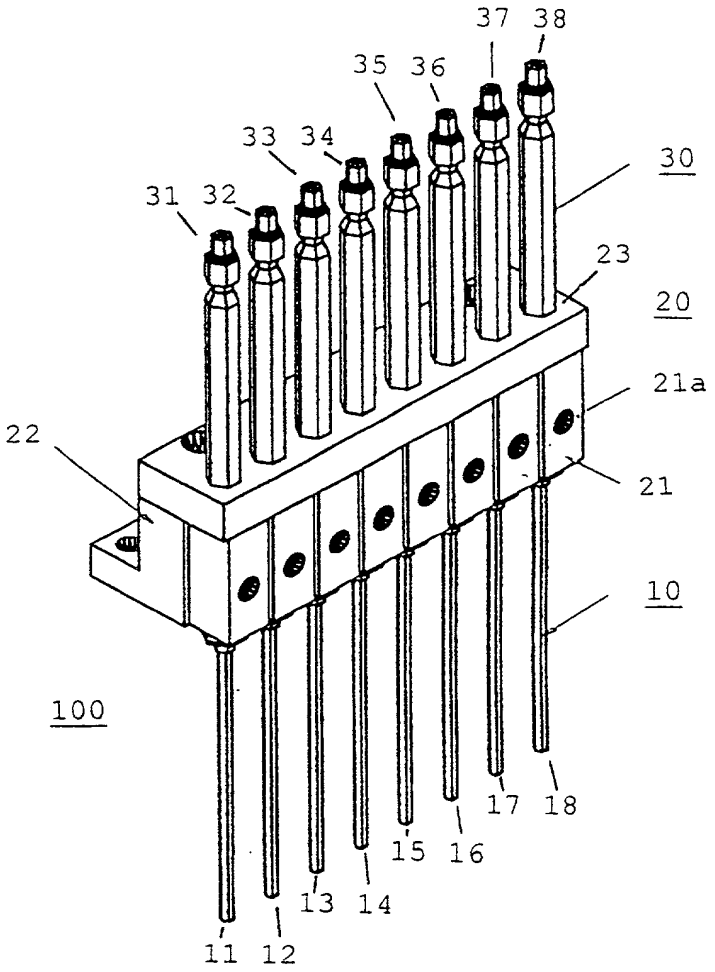
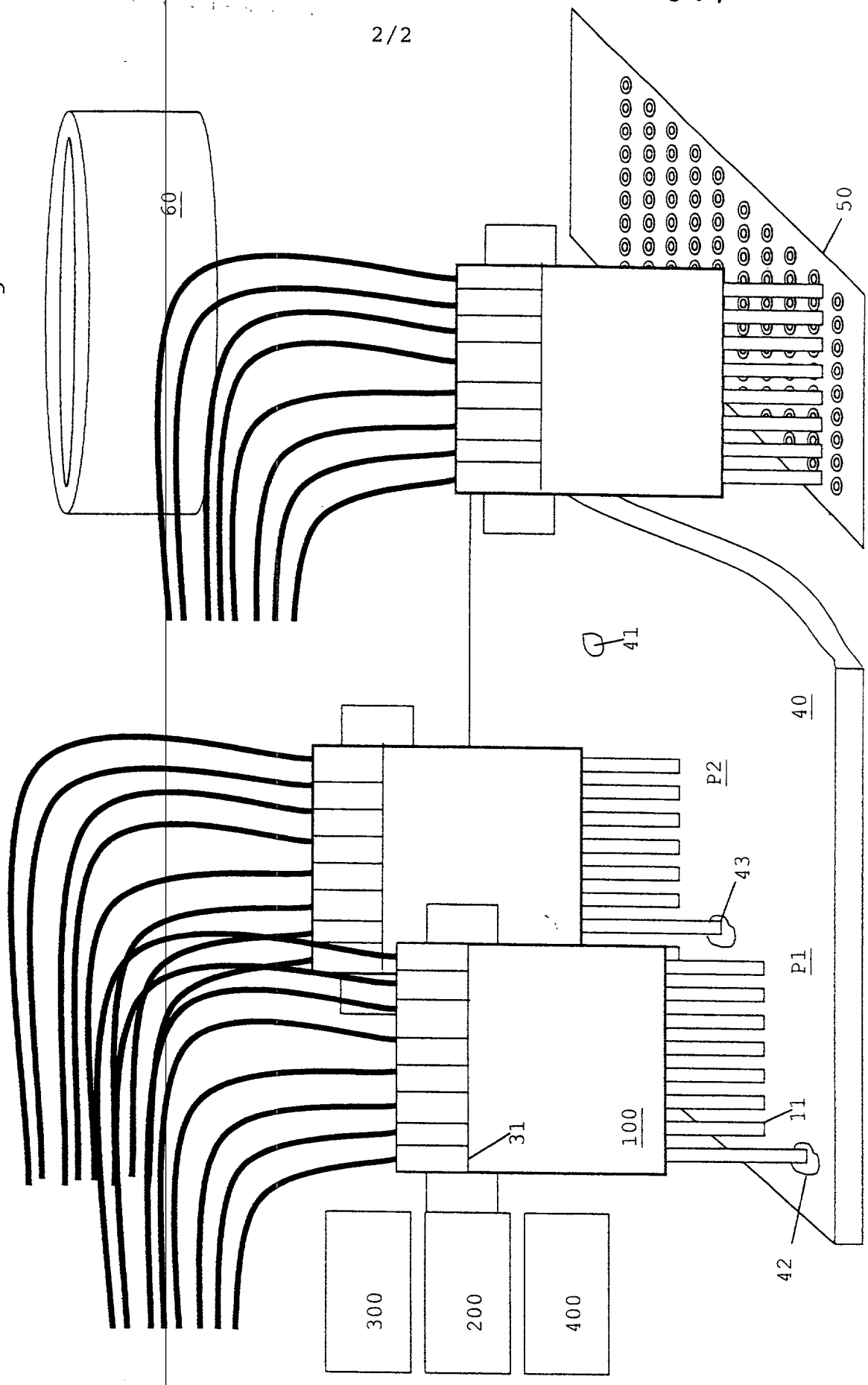

37
38
35
36
33
34
31
32
30
23
20
21a
22
21
10
100
17
18
15
16
13
14
11
12

Fig. 1

Fig. 2



1461105

PATENT

Attorney Docket No. 113737.5

COMBINED DECLARATION AND POWER OF ATTORNEY

My residence, post office address, and citizenship are as stated below next to my name.

I believe I am the original, first, and sole inventor (if only one name is listed below) or an original, first, and joint inventor (if multiple names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **APPARATUS AND METHOD FOR TAKING SAMPLES FROM POLYMER SUPPORT MATERIALS .**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

PRIORITY CLAIM

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

(Number)	(Country)	(Day/Month/Year Filed)	(Priority Claimed)
PCT/EP/99/02059	PCT	26/3/99	X Yes ___No
19815400.3	Germany	06/04/98	X Yes ___No
___	___	___	___Yes ___No

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material

information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorneys jointly and each of them severally, with full power of substitution, delegation, and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, and to transact all business in the Patent and Trademark Office connected therewith:

Robert A. Koons	Reg. No. 32,474
Matthew P. McWilliams	Reg. No. 46,922

I hereby direct that all correspondence and telephone calls in connection with this application be addressed to:

Robert A. Koons, Jr.
PEPPER HAMILTON LLP
3000 Two Logan Square
Eighteenth and Arch Streets
Philadelphia, PA 19103-2799
Telephone: (215) 981-4406
Facsimile: (215) 981-4271

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURES

100

Full name of **first inventor**: Christine Gauss
Inventor's signature X Christine Gauss

Date ✓ 02.11.00 Country of Citizenship Germany

Residence ~~Isaraustrasse 19A, D-82538 Geretsried~~, Germany DEX
STARNBERGER STR. 401b, D-82069 HOHENSCHÄFTLARN-NEUFAHRN

Full name of **second inventor**: Martin Horn
Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Karolinger Platz 1A, D-14052 Berlin, Germany

Full name of **third inventor**: Markus Kalkum

Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Koertestrasse 19, D-10967 Berlin, Germany

Full name of **fourth inventor**: Holger Eickhoff

Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Luetzelsteiner Weg 50, D-14195 Berlin, Germany

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURES

Full name of **first inventor**: Christine Gauss
Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Isaraustrasse 19A, D-82538 Geretsried, Germany

Full name of **second inventor**: Martin Horn
Inventor's signature x _____

Date x 30.10.00 Country of Citizenship Germany DEX

Residence ~~Karolinger Platz 1A, D-14052 Berlin, Germany~~
ALBERTINEN STR. 11, D-14165 BERLIN, GERMANY

Full name of **third inventor**: Markus Kalkum

Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Koertestrasse 19, D-10967 Berlin, Germany

Full name of **fourth inventor**: Holger Eickhoff
Inventor's signature x Holger Eickhoff

Date x 30.10.00 Country of Citizenship Germany

Residence ~~Luetzelsteiner Weg 50, D-14195 Berlin, Germany~~
TAYLORSTR. 7A, D-14195 BERLIN, GERMANY DEX

punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURES

Full name of **first inventor**: Christine Gauss
Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Isaraustrasse 19A, D-82538 Geretsried, Germany

Full name of **second inventor**: Martin Horn
Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Karolinger Platz 1A, D-14052 Berlin, Germany

3300

Full name of **third inventor**: Markus Kalkum

Inventor's signature X Markus Kalkum

Date 11/6/2000 Country of Citizenship Germany

Residence ~~Koertestrasse 19, D-10967 Berlin, Germany~~
Oedekovener Straße 10, D-53123 Bonn, Germany DEX

Full name of **fourth inventor**: Holger Eickhoff

Inventor's signature _____

Date _____ Country of Citizenship Germany

Residence Luetzelsteiner Weg 50, D-14195 Berlin, Germany